**National Advisory Committee (NAC)**
**for Acute Exposure Guideline Levels (AEGLs) for Hazardous Substances**

**December 10-12, 2003**

# Draft Meeting-31 Highlights

La Mansion Del Rio
San Antonio, Texas

## INTRODUCTION

Mr. Eric Stephens, Director of the Air Force Institute for Operational Health (AFIOH) welcomed the group to San Antonio and presented an overview of the AFOIH mission and the relevance of the AEGL process (Attachment 1). Mr. George Irving of Core 6 Solutions also welcomed the group and explained meeting logistics.

Ernie Falke announced that the AEGL public internet site should be up by January 5, 2004. The site will include proposed, interim, and final AEGL values, and .pdf files of the final documents; these files will be provided by the National Academy of Sciences and will be posted on the site. Ernie Falke also introduced Marquea King, a toxicologist on the EPA staff who is now working with the AEGL program.

The draft NAC/AEGL-30 meeting highlights were reviewed. Bob Benson pointed out that text was missing from the carbon monoxide discussion. Several committee members were concerned that no discussion was presented in the meeting summary text explaining the relationship of derived AEGL values for styrene, propane, and butane to the Lower Explosive Limit (LEL); explanation had only been included in the table footnotes. It was decided that the meeting highlights should be revised to include the LEL explanation in the text, while also maintaining the table footnotes. George Alexeeff pointed out that the AEGL-1 for propane was based on a NOAEL for vertigo; this needs to be added to the meeting summary. Marquea King explained that during NAC/AEGL-30, the AEGL-1 values for acetone cyanohydrin were not rounded correctly (AEGL-1 values were obtained by doubling the former AEGL-1 values after removing the modifying factor). The correct values should be 2.1 ppm (instead of 2.2 ppm) for the 10- and 30-min values and 0.69 ppm (instead of 0.70 ppm) for the 8-hour value. This modification was approved unanimously by a voice vote. A motion was made by John Hinz and seconded by Richard Thomas to accept the meeting highlights as presented with the aforementioned revisions. The motion passed unanimously by a voice vote. The final version of the NAC/AEGL-30 meeting highlights is attached (Appendix A) and was distributed to the NAC/AEGL by e-mail.

The highlights of the NAC/AEGL-31 meeting are summarized below along with the Meeting Agenda (Attachment 2) and the Attendee List (Attachment 3). The subject categories of the highlights do not necessarily follow the order listed in the NAC/AEGL-31 Agenda.

## RESPONSES TO *FEDERAL REGISTER* COMMENTS ON THE PROPOSED AEGL VALUES

Comments from the *Federal Register Notice* of July 18, 2003, on the proposed AEGL values for ammonia, xylenes, and methyl ethyl ketone were reviewed and discussed. The NAC/AEGL deliberation of these chemicals are briefly summarized as the following:

### Ammonia (CAS No. 7664-41-7)

**Chemical Manager: Larry Gephart, ExxonMobil**
**Staff Scientist: Kowetha Davidson, ORNL**

Comments were received from William C. Herz (Director of Scientific Programs, The Fertilizer Institute (TFI)), Mary Lee Hultin (Michigan Department of Environmental Quality), George Alexeeff, and John Morawetz. TFI commented on AEGL-1, -2, and -3 values; comments concerned the consistency of points of departure with the AEGL definitions, over-application of uncertainty factors (UF), time-scaling to 4- and 8-hour exposure durations, and potential for incorrect interpretation and regulatory misuse of AEGLs. Dr. Hultin commented that points of departure appeared to be based on appropriate science; however, concern was expressed regarding the selection of the intraspecies UF of only 1. Dr. Alexeeff and Mr. Morawetz both expressed concern regarding AEGL-2 and AEGL-3 values and the use of an intraspecies UF on 1. Kowetha Davidson responded to the scientific issues raised by these comments (Attachment 4). Dr. William Herz (Director of Scientific Programs for The Fertilizer Institute) also participated in the discussion and thanked the NAC for their thorough consideration of the comments. Dr. Davidson then proposed revising the AEGL-1 values (Attachment 5) from 25 ppm at all time points to 50 ppm at all time points based on moderate irritation in humans. After considerable discussion, a motion was made by Nancy Kim and seconded by Tom Hornshaw to adopt AEGL-1 values of 30 ppm for all time points based on very mild irritation in humans exposed to ammonia for 10 minutes. The motion passed (YES: 15; NO: 0; ABSTAIN: 3) (Appendix B). A motion was then made by Ernest Falke and seconded by George Rodgers to have no further discussion regarding AEGL-2 or AEGL-3 and to elevate the ammonia TSD to interim status. The motion passed (YES: 16; NO: 1; ABSTAIN: 0) (Appendix B).

| SUMMARY OF INTERIM AEGL VALUES FOR AMMONIA [ppm (mg/m$^3$)] | | | | | | | |
|---|---|---|---|---|---|---|---|
| Classification | Exposure Duration | | | | | | Endpoint (Reference) |
| | 5 min | 10 min | 30 min | 1 hour | 4 hours | 8 hours | |
| AEGL-1 (Nondisabling) | 30 (20) | 30 (20) | 30 (20) | 30 (20) | 30 (20) | 30 (20) | Very mild irritation (MacEwen et al., 1970); Verberk, 1977 |
| AEGL-2 (Disabling) | 380 (266) | 270 (189) | 160 (112) | 110 (77) | 110 (77) | 110 (77) | Irritation: eyes and throat; urge to cough (Verberk, 1977) |
| AEGL-3 (Lethal) | 3800 (2657) | 2700 (1890) | 1600 (1119) | 1100 (769) | 550 (385) | 390 (273) | Lethality (Kapeghian et al., 1982; MacEwen and Vernot, 1972) |

## Xylenes (CAS No. 1330-20-7)

**Chemical Manager: Bob Benson, EPA**
**Staff Scientist: Claudia Troxel, ORNL**

Comments were received from George Alexeeff, United Auto Workers (UAW) International Union, Clean Channel Association, Michigan Department of Environmental Quality (DEQ), and The American Chemistry Council (ACC). Dr. Alexeeff's comments suggested revising AEGL-1, -2, and -3 derivation descriptions to improve clarity. The UAW comments also concerned clarity in the derivation of AEGL-1 and AEGL-2 values, in addition to health effects noted at AEGL-2 and AEGL-3 concentrations being consistent with the AEGL definitions. The Clean Channel Association commented on needed notation when AEGL values approach the Lower Explosive Limit (LEL). The Michigan DEQ and the ACC both commented on the need to more thoroughly explain why separate AEGL values were not derived for individual xylene isomers. Claudia Troxel responded to issues raised by these comments (Attachment 6) and provided the committee with a revised text of the Summary and derivation sections of the TSD (Attachment 7). Dr. Troxel then discussed using PBPK modeling to refine the derived AEGL values (Attachment 8), pointing out that there is a flaw in the current TSD in that the assumption is made that a human and rat exposed to the same external xylene concentration will have the same internal dose. However, the rat will actually experience a greater xylene dose due blood: air partitioning and greater ventilation rate. Discussion then focused on whether to use modeling as support for values derived by SOP methodologies or to derive values based on modeling. After considerable discussion, a motion was made by Ernest Falke and seconded by Richard Thomas to accept AEGL-2 values of 1100 ppm for 10-min, 600 ppm for 30-min, and 400 ppm for 1-, 4-, and 8-hours based on PBPK modeling suggesting that values are below the threshold for CNS depression at 2 hours (Carpenter et al., 1975). Values were based on exposure at 50W of work for 10 and 30 minutes and 1 hour, and then held constant for the 4- and 8-hour time points because it was assumed that it is unlikely that any individual could maintain 50W work for 4 to 8 hours. An intraspecies UF of 3 was applied. The motion passed (YES: 14; NO: 1; ABSTAIN: 1)

(Appendix C). A motion was then made by Bob Benson and seconded by Ernest Falke to accept AEGL-3 values of 3300 ppm for 10-min, 1700 ppm for 30-min, and 1100 ppm for 1-, 4-, and 8-hours based on PBPK modeling with the endpoint of no lethality in rats exposed for 4 hours. Values again were based on exposure at 50W of work for 10 and 30 minutes and 1 hour, and then held constant for the 4- and 8-hour time points because it was assumed that it is unlikely that any individual could maintain 50W work for 4 to 8 hours. An intraspecies UF of 3 was applied. The motion passed (YES: 13; NO: 0; ABSTAIN: 3) (Appendix C). It was decided to pass the xylene values, but it was agreed that xylenes could come back to the committee if refinements on the PBPK model need to be made, particularly regarding the physiological parameters used for work.

| **Summary of Proposed AEGL Values for Xylenes (ppm)** | | | | | | |
|---|---|---|---|---|---|---|
| **Classification** | **10-minute** | **30-minute** | **1-hour** | **4-hour** | **8-hour** | **Endpoint (Reference)** |
| **AEGL–1 (Nondisabling)** | **130** | **130** | **130** | **130** | **130** | **Eye irritation in human volunteers exposed to 400 ppm mixed xylenes for 30 minutes (Hastings et al., 1986)** |
| **AEGL–2 (Disabling)** | **1100** | **600** | **400** | **400** | **400** | **Rats exposed to 1300 ppm mixed xylenes for 4 hours exhibited poor coordination (Carpenter et al., 1975)** |
| **AEGL–3 (Lethal)** | **3300** | **1700** | **1100** | **1100** | **1100** | **Rats exposed to 2800 ppm for 4 hours exhibited prostration followed by a full recovery (Carpenter et al., 1975)** |

**Methyl Ethyl Ketone (CAS No. 79-93-3)**

**Staff Scientist: Sylvia Talmage, ORNL**
**Chemical manager: Bill Bress, ASTHO**

Sylvia Talmage presented brief responses to comments to the Federal Register made by George Alexeeff, John Morawetz, the Michigan Department of Environmental Quality, and the Clean Channel Association (Attachment 9). New data, published since the development of AEGL values for methyl ethyl ketone (MEK) in December, 2001 and relevant to development of AEGL-1 values, were then discussed (Attachment 10). Based on three recent, well-conducted studies (Shibata et al. 2002; Muttray et al. 2002; Seeber et al. 2002) and the previously considered study of Dick et al. (1992), in which no irritation was reported at 200 ppm in healthy subjects, including subjects with self-reported multiple chemical sensitivity, the AEGL-1 was raised from 100 to 200

ppm. The motion to change the value was made by Loren Koller and seconded by Ernest Falke. The motion passed (YES:9 ; NO :3; ABSTAIN: 5 ) (Appendix D).

Prior to the meeting, a NAC member raised the question of whether the constant AEGL-2 value of 1700 ppm across time was realistic based on the fact that MEK reaches equilibrium in the blood fairly rapidly. The 1700 ppm value had been based on a 6 hr/day subchronic study with rats (Cavender et al. 1983). The endpoint was the threshold for narcosis. Several options were presented for time scaling. The NAC decided to time-scale the 1700 ppm concentration back to 10 minutes using the default value of n = 3. The 8-hour value was kept at 1700 ppm. The motion was made by Steve Barbee and seconded by John Hinz to time scale the values back to 10 minutes. The motion passed (YES: 13 ; NO: 0 ; ABSTAIN: 4 ) (Appendix D).

Sylvia Talmage then reported that the AEGL-3 10- and 30-minute value of 10,000 ppm had been based on a projected rather than a measured concentration (Hansen et al. 1992). Because two additional studies supported the derived value (Klimisch 1988; Zakhari 1977), she suggested keeping the value, but revising the basis. The suggestion was accepted by voice vote. A motion was made by Loren Koller and seconded by John Hinz to elevate methyl ethyl ketone to interim status. The motion passed (Appendix D).

**Summary of Interim AEGL Values for Methyl Ethyl Ketone**

| Classification | 10-minute | 30-minute | 1-hour | 4-hour | 8-hour | Endpoint (Reference) |
|---|---|---|---|---|---|---|
| AEGL–1 | 200 ppm | 200 ppm | 200 ppm | 200 ppm | 200 ppm | NOAEL for subjective symptoms - humans (Dick et al. 1992; Shibata et al. 2002; Muttray et al. 2002; Seeber et al. 2002) |
| AEGL–2 | 4900 ppm* | 3400 ppm* | 1700 ppm | 1700 ppm | 1700 ppm | Threshold for narcosis - rats (Cavender et al. 1983) |
| AEGL–3 | see below [a]# | see below [a]# | 4000 ppm[b]* | 2500 ppm[b]* | 2500 ppm[b]* | Threshold for lethality - rat, mouse (Klimisch 1988; Zakhari 1977; La Belle and Brieger 1955) |

[a]Based on Klimisch (1988); Zakhari (1977).
[b]Based on La Belle and Brieger (1955).
*: Concentrations are higher than 1/10 of the lower explosive limit of methyl ethyl ketone in air (1.8% = 18,000 ppm). Therefore, safety considerations against the hazard of explosion must be taken into account.
#: The AEGL-3 value of 10,000 ppm (29,300 mg/m$^3$) for 10 and 30 minutes is higher than 50% of the lower explosive limit of methyl ethyl ketone in air (1.8% = 18,000 ppm). Therefore, extreme safety considerations against the hazard of explosion must be taken into account.

## REVISIT OF CHEMICALS WITH SPECIFIC ISSUES

**Acrylic Acid (CAS No. 79-10-7)**

**Chemical Manager: Ernest Falke, U.S. EPA**
**Staff Scientist: Peter Griem, FOBIG**

Ernest Falke, Chemical Manager, explained a discrepancy between interim AEGL-2 values approved by the NAC and AEGL-2 values presented to the COT subcommittee (Attachment 11). This discrepancy resulted because the interim AEGL-2 values approved by the NAC were based on olfactory epithelial histopathology observed in monkeys and rats exposed to 75 ppm acrylic acid for *3 hours*, and the values presented to the COT subcommittee were based on similar histopathology noted in monkeys and rats exposed to 75 ppm for *6 hours*. After considerable discussion, a motion was made by Bob Benson and seconded by Loren Koller to reaffirm the AEGL-2 values based on the 3 hour point of departure and to revise the rationale to include concern about irreversibility of the histopathological lesions at the 6 hour time point. The motion passed (YES: 17; NO: 0; ABSTAIN: 0) (Appendix E).

**Uranium Hexafluoride (CAS No. 7783-81-5)**

**Chemical Manager: George Rusch, Honeywell**
**Staff Scientist: Cheryl Bast, ORNL**

George Rusch, Chemical Manager, explained a discrepancy between interim AEGL-3 values approved by the NAC and AEGL-3 values presented to the COT subcommittee (Attachment 12). This discrepancy resulted because the interim AEGL-3 values utilized a time-scaling exponent 'n' of 0.66, derived from rat lethality data ranging from 2- to 60-min, and the AEGL-3 values presented to the COT subcommittee utilized an n=1 (0.66 value rounded up). Using n=0.66 yielded 10- and 30-minute AEGL-3 values for uranium hexafluoride where exposure to HF alone approached the hydrogen fluoride AEGL-3 values. (Uranium hexafluoride hydrolyzes to hydrogen fluoride and uranyl oxyfluoride, so exposure to UF6 may actually represent an exposure to both hydrolysis products). Therefore, a proposal was made to utilize an 'n' of 1 (rounded up from 0.66) to scale AEGL-3 values across time. This provides more protective 10- and 30-minute AEGL-3 values. The 4- and 8-hour AEGL-3 values are slightly increased, but still considered protective. Also, the use of an 'n' of 1 for extrapolating from 1-hr to 4- and 8-hr is consistent with the NAC Standing Operating Procedures (SOP) default approach. A motion was made by George Alexeeff and seconded by George Rodgers to adopt AEGL-3 values of 220 $mg/m^3$ for 10-min, 72 $mg/m^3$ for 30-min, 36 $mg/m^3$ for 1-hr, 9.0 $mg/m^3$ for 4-hr, and 4.5 $mg/m^3$ for 8-hr. The motion passed (YES: 17; NO: 0; ABSTAIN: 0) (Appendix F).

# REVIEW of PRIORITY CHEMICALS

## Hydrogen Iodide (CAS No. 10034-85-2)

**Staff Scientist: Sylvia Talmage, ORNL**
**Chemical manager: Ernie Falke, U.S. EPA**

Sylvia Talmage discussed the poor database for hydrogen iodide (Attachment 13). In the absence of inhalation data for derivation of AEGL values for hydrogen iodide, the options were to either not derive values or base the values on the most chemically similar hydrogen halide, hydrogen bromide. Richard Niemeier stated that there is a need for AEGL values for hydrogen iodide. A motion was made by Richard Niemier and seconded by John Hinz to adopt the hydrogen bromide values as the values for hydrogen iodide, and to combine both chemicals into one document, with a clear presentation of the fact that data are unavailable for hydrogen iodide, and, in the absence of data, the values for hydrogen bromide should be consulted. The motion passed (YES: 12; NO: 5; ABSTAIN: 0) (Appendix G).

**Summary of AEGL Values for Hydrogen Bromide/Hydrogen Iodide[a]**

| Classification | 10-minute | 30-minute | 1-hour | 4-hour | 8-hour | Endpoint (Reference) |
|---|---|---|---|---|---|---|
| AEGL–1 | 1 ppm | 1 ppm | 1 ppm | 1 ppm | 1 ppm | Nose irritation in humans (CT Dept. Health 1955) |
| AEGL–2 | 100 ppm | 43 ppm | 22 ppm | 11 ppm | 11 ppm | Based on analogy with hydrogen chloride |
| AEGL–3 | 740 ppm | 250 ppm | 120 ppm | 31 ppm | 31 ppm | Threshold for lethality - rat (MacEwen and Vernot 1972) |

[a] These values were derived based on empirical human and animal data for hydrogen bromide and other hydrogen halides. In the absence of inhalation data for hydrogen iodide, the values for hydrogen bromide should be consulted. Based on structure-activity relationships for the hydrogen halides, it is believed that hydrogen iodide is less toxic than hydrogen bromide. Therefore, application of the hydrogen bromide values for hydrogen iodide is conservative.

## Sulfur Dichloride (CAS No. 10545-99-0)

**Chemical Manager: Ernest Falke, U.S. EPA**
**Staff Scientist: Kowetha Davidson, ORNL**

Kowetha Davidson presented information explaining that there are no human or animal data available to derive AEGL values for sulfur dichloride (Attachment 14). The chemical was placed in holding status (Appendix H).

## Sulfur Chloride (CAS No. 10025-67-9)

**Chemical Manager: Ernest Falke, U.S. EPA**
**Staff Scientist: Kowetha Davidson, ORNL**

Kowetha Davidson reviewed the available data for sulfur chloride (Attachment 15). Data are limited to one rat study (Bomhard et al., 2000). After discussion, the chemical was placed in holding status (Appendix H), and an attempt will made to contact the study author to determine if more experimental detail can be obtained.

## Chloroacetyl Chloride (CAS No. 79-04-9)

**Chemical Manager: Steven Barbee, Arch Chemical**
**Staff Scientist: Sylvia Milanez, ORNL**

The chemical review on chloroacetyl chloride was presented by Sylvia Milanez (Attachment 16). The proposed AEGL-1 values were based on mild eye irritation in rats exposed to 1 ppm chloroacetyl chloride for 6 hours (Dow, 1982). Intraspecies and interspecies UFs of 3 each (total UF = 10) were proposed because eye conjunctivitis due to local irritation is not expected to vary greatly between or within species. The proposed AEGL-1 value of 0.08 ppm was kept constant at all time points because mild irritant effects do not vary greatly over time.

The proposed AEGL-2 values were based on eye lacrimation and squinting (impaired ability to escape) in rats exposed to 32 ppm chloroacetyl chloride for 1 hour (Dow, 1986). An intraspecies UF of 3 was proposed to protect sensitive individuals, and an interspecies UF of 10 was proposed because data suggest humans are more susceptible to lacrimation than animals. Time scaling using n=3 for <1 hour and n=1 for >1 hour was proposed, except that the 4-hour value should be adopted as the 8-hour value because time scaling yields an 8-hour AEGL-2 value approaching the AEGL-1 value. Proposed AEGL-2 values were 1.9 ppm for 10-min, 1.3 ppm for 30-min, 1.1 ppm for 1-hour, and 0.27 ppm for 4- and 8-hours.

The proposed AEGL-3 values are based on an estimated lethality threshold of 215 ppm in rats (1/3 of the 1-hr rat $LC_{50}$ value) (Dow, 1986). An intraspecies UF of 3 was proposed to protect sensitive individuals, and an interspecies UF of 3 was proposed because rat and mouse lethality studies suggest a steep concentration-response curve at concentrations within a factor of 2-3. Time scaling using n=3 for <1 hour and n=1 for >1 hour was proposed. Proposed AEGL-3 values were 39 ppm for 10-min, 27 ppm for 30-min, 21 ppm for 1-hour, 5.4 ppm for 4-hours, and 2.7 ppm for 8-hours.

After much discussion, a motion was made by John Hinz and seconded by Bob Benson to accept the AEGL-1 values as proposed (0.08 ppm for all time periods). The motion did not pass (YES: 11; NO: 6; ABSTAIN: 1) (Appendix I). A motion was then made by George Alexeeff and seconded by Richard Niemier to adopt the AEGL-1 values as proposed with a modifying factor of

2 applied (0.04 ppm for all time points. This motion passed (YES: 11; NO: 4; ABSTAIN: 3) (Appendix I). A motion was then made by Bob Benson and seconded by John Hinz to adopt AEGL-2 values of 2.9 ppm for 10-min, 2.0 ppm for 30-min, 1.6 ppm for 1-hour, 0.40 ppm for 4-hours, and 0.20 ppm for 8-hours. The point of departure is that proposed above (32 ppm, 1-hr); however, inter- and intraspecies UFs of 3 each are applied and a MF of 2 (LOAEL to NOAEL) is also applied. Time scaling using n=3 for <1 hour and n=1 for >1 hour was proposed. The motion passed (YES: 10; NO: 4; ABSTAIN: 3) (Appendix I). A motion was then made by Bob Benson and seconded by John Hinz to adopt AEGL-3 values of 95 ppm for 10-min, 66 ppm for 30-min, 50 ppm for 1-hour, 13 ppm for 4-hours, and 6.5 ppm for 8-hours. The point of departure is the highest concentration (522 ppm) causing no deaths in rats exposed for 1 hour (Dow, 1986); inter- and intraspecies UFs of 3 each are applied. Time scaling using n=3 for <1 hour and n=1 for >1 hour was proposed. The motion passed (YES: 13; NO: 2; ABSTAIN: 3) (Appendix I).

| Summary of AEGL Values for Chloroacetyl chloride | | | | | | |
|---|---|---|---|---|---|---|
| **Classification** | **10-minute** | **30-minute** | **1-hour** | **4-hour** | **8-hour** | **Endpoint (Reference)** |
| AEGL–1 | 0.04 ppm | 0.04 ppm | 0.04 ppm | 0.04 ppm | 0.04 ppm | Eye irritation in rats (Dow, 1986) |
| AEGL–2 | 2.9 ppm | 2.0 ppm | 1.6 ppm | 0.40 ppm | 0.40 ppm | Lacrimation and squinting in rats (Dow, 1986) |
| AEGL–3 | 95 ppm | 66 ppm | 50 ppm | 13 ppm | 6.5 ppm | Highest concentration causing No deaths in rats (Dow, 1986) |

## Dichloroacetyl Chloride (CAS No. 79-36-7)

**Chemical Manager: Steven Barbee, Arch Chemical**
**Staff Scientist: Sylvia Milanez, ORNL**

The chemical review on dichloroacetyl chloride was presented by Sylvia Milanez (Attachment 16). AEGL-1 values were not recommended due to insufficient data.

The proposed AEGL-2 values were based on coughing and notable discomfort in workers exposed to 1.6 ppm dichloroacetyl chloride for an estimated duration of 10 min (Dahlberg and Myrin, 1971). An intraspecies UF of 3 was proposed to protect sensitive individuals, because coughing and notable discomfort is not likely to be significantly worst in the general population than in repeatedly exposed workers. Time scaling using n=1 scaling from 10-min to 30 min and maintaining the same value from 30-min to 8-hr was proposed, because scaling to 1-, 4-, and 8-hour time periods yielded concentrations below those recognized by workers. Proposed AEGL-2 values were 0.53 ppm for 10-min, and 0.18 ppm for 30-min, 1-, 4-, and 8-hours.

The proposed AEGL-3 values are based on an estimated 4-hour lethality threshold of 500 ppm in rats (Smyth et al., 1951). An intraspecies UF of 10 because the cause of death in the key study was unknown and variability among humans cannot be reliably estimated. An interspecies UF of 10 was proposed because only one species was tested and the cause of death was unknown. Time scaling using n=3 for <4 hours and n=1 for >4 hours was proposed, except that the 30-min value should be adopted as the 10-min value. Proposed AEGL-3 values were 10 ppm for 10-min and 30-min, 7.9 ppm for 1-hour, 5.0 ppm for 4-hours, and 2.5 ppm for 8-hours.

After much discussion, a motion was made by Bob Benson and seconded by Loren Koller to not recommend AEGL-1 because of insufficient data. The motion passed (YES: 16; NO: 0; ABSTAIN: 0) (Appendix J). A motion was then made by Bob Benson and seconded by Ernest Falke to accept the AEGL-3 values as proposed. This motion did not pass. After considerable discussion concerning the relative toxicity of chloroacetyl chloride and dichloroacetyl chloride, a motion was made by George Alexeeff and seconded by Richard Thomas for AEGL-3 to combine the dichloroacetyl chloride TSD with the chloroacetyl chloride TSD, explain that dichloroacetyl chloride is less toxic than chloroacetyl chloride, and recommended adopting chloroacetyl chloride values for dichloroacetyl chloride. The motion passed (YES: 15; NO: 0; ABSTAIN: 1) (Appendix J). A motion was then made by Steve Barbee and seconded by Bill Bress to adopt chloroacetyl chloride AEGL-2 values as the AEGL-2 values for dichloroacetyl chloride, and combining the TSDs as was done for AEGL-3. The motion passed (YES: 14; NO: 0; ABSTAIN: 2) (Appendix I). A motion was then made by Richard Thomas and seconded by Loren Koller to reopen the AEGL-1 discussion; this motion passed by a show of hands. A motion was then made by Ernest Falke and seconded by Loren Koller to adopt the chloroacetyl chloride AEGL-1 values as the AEGL-1 values for dichloroacetyl chloride and present in the combined TSD. The motion passed (YES: 15; NO: 0; ABSTAIN: 1) (Appendix J).

## Trichloroacetyl Chloride (CAS No. 76-02-8)

**Chemical Manager: Steven Barbee, Arch Chemical**
**Staff Scientist: Sylvia Milanez, ORNL**

The chemical review on trichloroacetyl chloride was presented by Sylvia Milanez (Attachment 16). AEGL-1, AEGL-2, and AEGL-3 values were not recommended due to insufficient data. A motion was made by Richard Thomas and seconded by Ernest Falke to not recommend AEGL-1, AEGL-2, or AEGL-3 values due to insufficient data and to include this information in the TSD for chloroacetyl chloride. The motion passed (YES: 16; NO: 0; ABSTAIN: 0) (Appendix K).

## Acetyl Chloride (CAS No. 75-36-5)

**Chemical Manager: Steven Barbee, Arch Chemical**
**Staff Scientist: Sylvia Milanez, ORNL**

The chemical review on acetyl chloride was presented by Sylvia Milanez (Attachment 16). AEGL-1, AEGL-2, and AEGL-3 values were not recommended due to insufficient data. A motion

was made by Ernest Falke and seconded by Richard Thomas to not recommend AEGL-1, AEGL-2, or AEGL-3 values due to insufficient data and to include this information in the TSD for chloroacetyl chloride. The motion passed unanimously by a show of hands (Appendix L).

## Tetrachloroethylene (CAS No. 127-18-4)

**Staff Scientist: Claudia Troxel, ORNL**
**Chemical Manager: Bill Bress, ASTHO**

Tetrachloroethylene will be discussed at a future meeting after modeling is completed.

## Oleum (CAS No. 8014-95-7)
## Sulfuric Acid (CAS No. 7664-93-9)
## Sulfur Trioxide (Cas No. 7446-11-9)

**Staff Scientist: Johan Schefferlie, Netherlands**
**Chemical Manager: Loren Koller**

Johan Schefferlie presented a progress report on sulfuric acid, sulfur trioxide, and oleum (Attachment 17). These three chemicals will be presented together in one TSD and values will be derived only for sulfuric acid. This TSD will be presented at a future NAC meeting.

## Methacrylonitrile (CAS No. 126-98-7)

**Staff Scientist: Cheryl Bast, ORNL**
**Chemical Manager: George Rodgers**

A brief history of the TSD and chemical review for methacrylonitrile was presented by Cheryl Bast (Attachment 18). The proposed AEGL-1 was based on transitory nasal, throat or ocular irritation in humans exposed to 2 ppm methacrylonitrile for 10 minutes (Pozzani et al., 1968). No uncertainty factor was applied to account for sensitive human populations because similar transitory irritation was noted in humans at 14 ppm. The 2 ppm concentration was held constant across the 10- and 30-minute, and 1-, 4-, and 8-hour exposure time points. This approach is considered appropriate since mild irritant effects generally do not vary greatly over time.

The proposed AEGL-2 was based on a 13-15% decrease in fetal body weight in rats exposed to 100 ppm methacrylonitrile 6 hours/day on gestation days 6-20 (Saillenfait et al., 1993). An uncertainty factor of 3 was applied to account for sensitive individuals. This uncertainty factor is considered sufficient because human accidental and occupational exposures indicate that there are individual differences in sensitivity to HCN (the metabolically-liberated toxicant) but the magnitude of these differences does not appear to be great (NRC, 2002). An interspecies uncertainty factor of 3 was also applied, because use of the full uncertainty interspecies factor of 10, would yield AEGL-2 values that are not consistent with the total data set. For time scaling, an *n* of 3 was applied to extrapolate to the 30-minute, 1-hour, and 4-hour time periods, and an *n* of 1 was applied to extrapolate to the 8-hour time period. The 30-minute value was adopted as the 10-minute value. Proposed AEGL-2 values were 22 ppm for 10- and 30-min, 18 ppm for 1-hr, 11 ppm for 4-hours, and 7.5 ppm for 8-hours.

The loss of consciousness, with no mortality noted, in rats exposed to 176 ppm for 3 hours was used as the basis of proposed AEGL-3 values (Pozzani et al., 1968). An uncertainty factor of 3 was applied to account for sensitive individuals, and interspecies uncertainty factor of 3 was also applied. Rationale for the UFs is the same as explained above for the AEGL-2 derivation. For time scaling, an *n* of 3 was applied to extrapolate to the 10-minute, 30-minute, 1-hour, and an n of 1 was used for extrapolation to the 4-hour time period. The 4-hour AEGL-3 value was also adopted as the 8-hour AEGL-3 value because time scaling would yield an 8-hour AEGL-3 value less that the 8-hour AEGL-2 value. The proposed AEGL-3 values were 32 ppm for 10-min and 30-min, 25 ppm for 1-hr, and 13 ppm for 4- and 8-hours.

After extensive discussion, a motion was made by George Rodgers and seconded by Loren Koller to accept the AEGL-3 values as presented. The motion passed (YES: 11; NO: 0; ABSTAIN: 3) (Appendix M). A motion was then made by Bob Benson and seconded by George Rodgers to derive AEGL-2 values by dividing AEGL-3 values by 2 (16 ppm for 10- and 30-min, 13 ppm for 1-hr, and 6.5 ppm for 4- and 8-hours). This approach is justified due to the relatively steep concentration-response curve, and dividing the AEGL-3 values by 3 (as per the SOP) for this chemical would yield AEGL-2 values in the range where only minor irritation was noted in humans. The motion passed (YES: 15; NO: 0; ABSTAIN: 1) (Appendix M). A motion was then made by George Rodgers and seconded by Loren Koller to adopt AEGL-1 values of 2.0 ppm for 10-min and 30-min, as proposed, and 1.0 ppm for 1-hr, 4-hr, and 8-hr due to the lack of human data beyond 10-minutes and the potential for a systemic effect. The motion passed (YES: 15; NO: 0; ABSTAIN: 1) (Appendix M).

| **Summary of AEGL Values For Methacrylonitrile [ppm (mg/m$^3$)]** | | | | | | |
|---|---|---|---|---|---|---|
| **Classification** | **10-Minute** | **30-Minute** | **1-Hour** | **4-Hour** | **8-Hour** | **Endpoint (Reference)** |
| AEGL-1 | 2.0 (5.5) | 2.0 (5.5) | 1.0 (2.8) | 1.0 (2.8) | 1.0 (2.8) | Transient nasal, throat, or ocular irritation in humans (Pozzani et al., 1968) |

| | | | | | | |
|---|---|---|---|---|---|---|
| AEGL-2 | 16 (44) | 16 (44) | 13 (35) | 6.5 (15) | 6.5 (15) | AEGL-3 ÷ 2 |
| AEGL-3 | 32 (88) | 32 (88) | 25 (69) | 13 (36) | 13 (36) | Loss of consciousness, no mortality in rats (Pozzani et al., 1968) |

**Benzonitrile (CAS No. 100-47-0)**

**Staff Scientist: Cheryl Bast, ORNL**
**Chemical Manager: George Rodgers**

The and chemical review for benzonitrile was presented by Cheryl Bast (Attachment 19).
The proposed AEGL-1 was based on irritation of extremities in rats exposed to 900 ppm for 1 hour (MacEwen and Vernot, 1974). An interspecies uncertainty factor of 10 was applied because the rat is not the most sensitive species. An uncertainty factor of 3 was applied to account for sensitive individuals. This intraspecies uncertainty factor of 3 is supported by the steep concentration-response curve, which implies little individual variability. A modifying factor of 2 was also applied to account for the sparse data base and potential delayed hepatic effects, such as the hepatic congestion evidenced in mice (MacEwen and Vernot, 1974). An *n* of 3 was applied to extrapolate to the 30-minute time period, and an *n* of 1 was applied to extrapolate to the 4- and 8-hour time periods. Proposed AEGL-1 values were 19 ppm for 10- and 30-min, 15 ppm for 1-hr, 3.8 ppm for 4-hours, and 2.0 ppm for 8-hours.

The proposed AEGL-2 was based on labored breathing and poor coordination in rats exposed to 900 ppm for 3 hours (MacEwen and Vernot, 1974). An interspecies uncertainty factor of 10 was applied because the rat is not the most sensitive species. An uncertainty factor of 3 was applied to account for sensitive individuals. This intraspecies uncertainty factor of 3 is supported by the steep concentration-response curve, which implies little individual variability. A modifying factor of 2 was applied to account for the sparse data base and to protect against potential delayed hepatic effects, such as the hepatic congestion evidenced in mice (MacEwen and Vernot, 1974). An *n* of 3 was applied to extrapolate to the 30-minute and 1-hour, time periods, and an *n* of 1 was applied to extrapolate to the 4- and 8-hour time periods. The 30-minute value was adopted as the 10-minute value. Proposed AEGL-2 values were 27 ppm for 10- and 30-min, 22 ppm for 1-hr, 11 ppm for 4-hr, and 5.6 ppm for 8-hr.

The exposure of mice to 890 ppm for 2 hours resulting in 1/7 deaths in mice was used as the basis of the proposed AEGL-3 values (MacEwen and Vernot, 1974). An interspecies uncertainty factor of 3 was applied, and an uncertainty factor of 3 was also applied to account for sensitive individuals. Uncertainty factor justifications are as described above for AEGL-2. A modifying factor of 2 was applied to account for the use of an endpoint where 1 of 10 animals died, the sparse data base, and to protect against potential delayed hepatic effects, such as the hepatic congestion evidenced in mice (MacEwen and Vernot, 1974). An *n* of 3 was applied to extrapolate to the 30-minute and 1-hour, time periods, and an *n* of 1 was applied to extrapolate to

the 4- and 8-hour time periods. The 30-minute value was adopted as the 10-minute value due to the added uncertainty of extrapolating from a 2-hour time point to 10-minutes. The proposed AEGL-3 values were 71 ppm for 10- and 30-min, 56 ppm for 1-hr, 23 ppm for 4-hr, and 11 ppm for 8-hr.

After discussion, a motion was made by Bob Benson and seconded by Ernest Falke to accept the AEGL-3 values as proposed except for the 10-min value which should be derived by time scaling per the SOP. Thus, the 10-min AEGL-3 value becomes 100 ppm. The motion passed (YES: 15; NO: 1; ABSTAIN: 0) (Appendix N). A motion was then made by George Rodgers and seconded by Bob Benson to accept the AEGL-2 values as proposed except for the 10-min value which should be derived by time scaling per the SOP. Thus, the 10-min AEGL-2 value becomes 39 ppm. The motion passed (YES: 14; NO: 2; ABSTAIN: 0) (Appendix N). A motion was then made by Bob Benson and seconded by Ernest Falke not to recommended AEGL-1 values due to the lack of data. The motion passed (YES: 16; NO: 0; ABSTAIN: 0) (Appendix N).

**Summary of AEGL Values for Benzonitrile**

| Classification | 10-minute | 30-minute | 1-hour | 4-hour | 8-hour | Endpoint (Reference) |
|---|---|---|---|---|---|---|
| AEGL-1 | NR | NR | NR | NR | NR | Insufficient data to derive AEGL-1 values |
| AEGL-2 | 39 (163) | 27 (113) | 22 (92) | 12 (50) | 5.5 (21) | Labored breathing, incoordination in rats (MacEwen and Vernot, 1974) |
| AEGL-3 | 100 (420) | 71 (298) | 56 (235) | 23 (97) | 11 (46) | 14% death in mice (MacEwen and Vernot, 1974) |

NR: Not Recommended.

## Special Presentation

George Woodall presented information on a comparative survey of acute inhalation health reference values (Attachment 20).

### Administrative Matters

The site and time of future meetings is as follows:

NAC/AEGL-32: April 19-21, 2004, Washington DC
NAC/AEGL-33: June 14-16, 2004, Netherlands

NAC/AEGL-34: September 21-23, 2004, Washington DC

All items in the agenda were discussed as thoroughly as the time permitted. The meeting highlights were prepared by Cheryl Bast and Sylvia Talmage, Oak Ridge National Laboratory, with input from the respective chemical managers, staff scientists, and other contributors.

## LIST OF ATTACHMENTS

The attachments were distributed during the meeting and will be filed in the EPA Docket Office.

Attachment 1. Overview of AFOIH
Attachment 2. NAC/AEGL-31 Meeting Agenda
Attachment 3. NAC/AEGL-31 Attendee List
Attachment 4. Response to Federal Register Comments for ammonia
Attachment 5. Proposed AEGL-1 revision for ammonia
Attachment 6. Response to Federal Register comments for xylenes
Attachment 7. Revised text for xylenes
Attachment 8. PBPK modeling for xylenes
Attachment 9. Response to Federal Register Comments for methyl ethyl ketone
Attachment 10. New AEGL-1 data for methyl ethyl ketone
Attachment 11. AEGL-2 issues for acrylic acid
Attachment 12. AEGL-3 time scaling issue for uranium hexafluoride
Attachment 13. Data Analysis of hydrogen iodide
Attachment 14. Data Analysis of sulfur dichloride
Attachment 15. Data Analysis of sulfur chloride
Attachment 16. Data Analysis of chloroacetyl chloride, dichloroacetyl chloride, trichloroacetyl chloride, and acetyl chloride
Attachment 17. Sulfuric acid, sulfur trioxide, and oleum progress report
Attachment 18. Data Analysis of methacrylonitrile
Attachment 19. Data Analysis of benzonitrile
Attachment 20. Comparative survey of acute inhalation health reference values

## LIST OF APPENDICES

Appendix A. Final meeting highlights of NAC/AEGL-30
Appendix B. Ballot for ammonia
Appendix C. Ballot for xylenes
Appendix D. Ballot for methyl ethyl ketone
Appendix E. Ballot for acrylic acid
Appendix F. Ballot for uranium hexafluoride
Appendix G. Ballot for hydrogen iodide
Appendix H. Ballots for sulfur dichloride and sulfur chloride
Appendix I. Ballot for chloroacetyl chloride
Appendix J. Ballot for dichloroacetyl chloride
Appendix K. Ballot for trichloroacetyl chloride
Appendix L. Ballot for acetyl chloride
Appendix M. Ballot for methacrylonitrile
Appendix N. Ballot for benzonitrile